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(54) METHOD FOR THE PRODUCTION OF A HYDROPHILIC POLYMER PRODUCT

- (71) We, SPECIAL POLYMERS LIMITED, c/o T. J. Newman & Co. Ltd., Bank Chambers, 214 Bishopsgate, London, E.C.2., a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—
- The invention relates to a method for the production of a hydrophilic polymer product. In the polymerisation of monomer materials by conventional means, polymerisation takes place by the agency of a chemical initiator and cross-linking can proceed by means of a cross-linking agent. One of the criteria for evaluating a hydrophilic polymer is the capacity of the polymer for absorbing water. A second criterion is the elimination of any chemical agent or residue of the polymerisation process likely to cause an unfavourable reaction in living tissue. These criteria are particularly important in respect of polymers for use in the production of ophthalmic devices such as contact lenses, prosthetic devices, and other devices for use in contact with living tissue. Further criteria include the mechanical durability and hydraulic and gas permeability of the polymer.
- Until now, difficulty has been encountered in providing polymers suitable for use in contact with living tissue. In particular, difficulty has been encountered in providing polymers which are capable of absorbing more than their own weight of water, with a low degree of chemical residue and sufficient mechanical strength.
- However, it has now been found that by subjecting hydrophilic monomer materials to electromagnetic radiation in the ultraviolet ray to gamma ray range, it is possible to obtain polymers capable of absorbing up to five times or more of their own weight of water. These polymers, moreover, are eminently suitable for use in contact with living tissue because they contain none of the harmful contaminants derived from the initiators used in conventional polymerisation.
- According to the invention there is provided a method for the production of a hydrophilic polymer product, which method comprises subjecting to polymerisation an initial mixture containing (1) at least one hydrophilic monomer selected from N-vinyl pyrrolidones, preferably N - vinyl - 2 - pyrrolidone, and hydroxyalkyl methacrylates, preferably 2 - hydroxyethyl methacrylate and hydroxypropyl methacrylates, particularly 2 - hydroxypropyl methacrylate, and at least one hydrophobic monomer selected from alkyl acrylates, alkyl methacrylates and styrene or (2) at least one of N - vinyl - 2 - pyrrolidone and hydroxyethyl methacrylate and at least one hydrophobic polymer selected from nylons, polyamides of terephthalic acid with one or more alkyl-substituted hexamethylene diamines, poly(alkyl acrylates), polyalkyl methacrylates, polystyrene, polyvinyl chloride and bisphenol A polycarbonate, the polymerisation being effected by means of electromagnetic radiation in the ultraviolet ray—gamma ray range in an environment free from any chemical polymerisation initiator and from any residue of such initiator.
- The polymer may, in particular circumstances, contain up to 90% by weight of the hydrophobic component but it generally contains not more than 40% by weight of the hydrophobic component.
- The preferred hydrophilic monomer is N - vinyl - 2 - pyrrolidone and preferred hydrophobic monomers include methyl methacrylate and methyl acrylate.
- The hydrophilic monomer material or combination of hydrophilic materials chosen can be varied so as to obtain polymer products

having different properties. Variation of the properties of the polymer product may also be effected by varying the particular hydrophobic material or materials used. Thus, the water uptake of the polymer product may be varied, by the control of the chemical composition of the initial mixture and the radiation treatment, to lie between one half of the dry weight of the polymer product and ten times the dry weight of the polymer product, while retaining mechanical properties and optical transparency consistent with its use as an ophthalmic device or biologically acceptable implant. Liquid and gas permeability in the hydrated state may be controlled both by radiation treatment and polymerisation in the presence of a chemically passive agent, such as water or glycerol, capable of extending or swelling the polymer product. When the hydrophilic and hydrophobic materials in the initial mixture consist solely of monomers, the weight ratio of the extending agent to the monomers may vary between 1:20 and 2:1 but is preferably between 1:10 and 1:1.

The colour of the polymer product may also be controlled by using suitable dyes in admixture with or included in the monomer material and polymerised *in situ* without complications of chemical initiator interaction or degradation common in conventional polymerisation processes. In the same way biologically active substances may be included, particularly therapeutic substances such as antibiotics, bactericides, fungicides, steroids, hormone preparations and other drugs, for example cetamide, tropicamide, idoxuridine and sulphacetamide sodium. Instead of including such ingredients during the polymerisation stage, they may be added by absorption from solution by hydrating the polymer product.

The properties of the polymer products may also be varied by varying the proportions of the monomers present and by varying the amount of radiation provided. The molar ratio of hydrophilic monomer to hydrophobic monomer may, for example, be between 10:1 and 1:2 but is preferably between 5:1 and 2:1.

When at least part of the hydrophobic material in the initial mixture is present as a polymer, that polymer may be a nylon such as nylon 6; nylon 6,6; nylon 6,10; nylon 11; or nylon 12; or a polyamide of terephthalic acid with one or more alkyl-substituted hexamethylene diamines such as a mixture of 2,2,4- and 2,4,4-trimethylhexamethylene diamines; or polymethyl methacrylate or polymethyl acrylate.

The weight ratio of the hydrophilic monomer to the hydrophobic polymer may be between 10:1 and 1:2, but is often dependent upon the solubility of the hydrophobic poly-

mer in the hydrophilic monomer. Preferably the weight ratio is between 5:1 and 1:1.

The hydrophobic polymeric material is dissolved in the hydrophilic monomer material, placed in a suitable mould, and exposed to the electromagnetic radiation, or the polymer may be irradiated alone and then contacted with the hydrophilic monomer. Graft polymerisation is initiated by quantities of long lived radicals trapped in the solid polymer. The resultant polymerised and possibly lightly cross-linked mass is a rigid hydrophilic transparent material of enhanced elasticity and physical properties.

It is understood that as a result of electromagnetic radiation, the molecules are ionised or radiolytic bond breaking produces free radicals so as to provide attachment sites at which the ionised molecules or free radicals are capable of attaching themselves to similarly ionised molecules or free radicals. By varying the amount of radiation, and thus the amount of ionisation, it has been found possible to control the formation of copolymer material and to control the extent of cross-linking between the polymer chains.

It has been observed that the water uptake, swelling capacity, tensile and tear strengths for a fixed hydrophobic unit to hydrophilic unit ratio [such as that between the polyamide of terephthalic acid and an alkyl-substituted hexamethylene diamine, for example a mixture of isomeric 2,2,4- and 2,4,4-trimethylhexamethylene diamines and N - vinyl - 2 - pyrrolidone, or that between a polyalkyl acrylate such as poly(methyl acrylate) and N - vinyl - 2 - pyrrolidone, or that between a poly(alkyl methacrylate) such as poly(methyl methacrylate) and N - vinyl - 2 - pyrrolidone, or that between an alkyl acrylate or methacrylate such as methyl acrylate or methyl methacrylate and N - vinyl - 2 - pyrrolidone] can be controlled by the addition of one or more di-functional or poly-functional compounds which act as cross-linking agents and can vary the cross-link density compared to that resulting from a given radiation dose. Suitable cross-linking agents include compounds containing at least 2 olefinic bonds per molecule, suitably divinylbenzene, allyl methacrylate and ethylene glycol dimethacrylate, in concentrations up to about twenty percent by weight of the total weight of monomer polymer mix but usually the desired effect can be obtained using concentrations between 0.01% by weight and 5% by weight of the total weight of mix.

If a polymer product suitable for forming into the desired article by moulding is required, the molecular weight of the polymer product formed can be controlled by the addition of a mutual solvent, i.e. compatible with the monomer system or the polymer/monomer system, such as acetone, carbon tetrachloride or ethanol. Adjustment of the

ratio of monomer to solvent controls monomer/monomer contacts and this affects the length of the polymer chains produced in the addition polymerisation process. By evaporation of the solvent or precipitation in a non-solvent followed by drying and grinding of the polymer product, suitable moulding materials are obtained. These can be cross-linked in the desired mould by addition of a cross-linking agent in a proportion up to 10% of the total polymer product weight, preferably between 1% and 5% by weight. Such material are diamines, such as hexamethylene diamine, or dianhydrides which on heating promote cross-linking by condensation reactions with such functional groups as hydroxyl or amide present in the structure of the polymer product.

The polymerisation is preferably effected in an oxygen-free atmosphere, for example under an inert atmosphere such as an atmosphere of nitrogen or a noble gas, or in vacuo.

A typical electromagnetic radiation having a quantum energy lying between 60 and 100 Mev, which is suitable for the present invention, is the gamma ray radiation from a Cobalt 60 source. The radiation dosage used is suitably from 2 to 5 MegaRads, for example 2.5 MegaRads.

The necessary dosage may be administered over any period between one and forty-eight hours, typically over a period of about nine hours.

The polymerisation conversion is generally at least 95% is preferably greater than 98%, and can be greater than 99.8%.

The invention is illustrated in the following Examples. The polymerisation was carried out in a tubular container made of polyethylene. The water uptake or absorption of the polymer product was determined by removing the cylindrical rod of solid polymer product from the tubular polyethylene container and cutting a disc 3 mm. thick from the central portion of the rod. The disc was weighed under anhydrous conditions and then immersed in saline solution (pH 7.3) and the uptake of water after immersion for specific periods was determined by reweighing after carefully blotting off all the surface water. The water absorbed was given as a percentage calculated as follows:—

$$\text{Percentage water absorbed} = \frac{(W_1 - W_0) 100}{W_0}$$

where W_0 is the weight of the disc before immersion and W_1 its weight after immersion.

The concentration of monomer left in the polymer product after polymerisation and consequently the polymerisation conversion was ascertained by gas-liquid chromatographic and ultra-violet spectrophotometry examinations of water and solvent washings from the polymer product.

graphic and ultra-violet spectrophotometry examinations of water and solvent washings from the polymer product.

Example 1

A mixture of 40 g. of freshly distilled N - vinyl - 2 - pyrrolidone and 10 g. of freshly distilled methyl methacrylate was purged with nitrogen and sealed in a polyethylene tube. The tube was subjected to a dose of 2.5 MegaRads of ionising radiation from a Cobalt 60 source. The solid polymer product (a copolymer) formed was very hard and transparent. The water absorption of the copolymer determined on a 3 mm. thick disc was 710% after immersion for one day, 920% after immersion for two days and 1040% after immersion for eleven days. The disc was transparent, light amber in colour, very flexible and strong, and greatly swollen after immersion for eleven days. The polymerisation conversion was found to be greater than 98%.

Example 2

A mixture of 30 g. of freshly distilled N - vinyl - 2 - pyrrolidone, 10 g. of freshly distilled methyl methacrylate and 0.4 g. of allyl methacrylate was purged with nitrogen and sealed in a polyethylene tube. The tube was subjected to a dose of 2.5 MegaRads of ionising radiation from a Cobalt 60 source. The solid copolymer formed was very hard and transparent. The water absorption of the copolymer determined on a 3 mm. thick disc was 250% after immersion for three days. The disc was transparent, light amber in colour, very flexible and strong, and greatly swollen after immersion for eleven days. The polymerisation conversion was found to be greater than 98%.

Example 3

A mixture of 20 g. of freshly distilled N - vinyl - 2 - pyrrolidone, 10 g. of freshly distilled methyl methacrylate and 0.15 g. of allyl methacrylate was purged with nitrogen and sealed in a polyethylene tube. The tube was subjected to a dose of 2.5 MegaRads of ionising radiation from a Cobalt 60 source. The solid copolymer formed was very hard and transparent. The water absorption of the copolymer determined on a 3 mm. thick disc was 240% after immersion for three days. The disc was transparent, light amber in colour, very flexible and strong, and greatly swollen after immersion for eleven days. The polymerisation conversion was found to be greater than 98%.

Example 4

A mixture of 25 g. of freshly distilled N - vinyl 2 - pyrrolidone, 10 g. of freshly distilled methyl methacrylate and 0.35 g. allyl methacrylate was purged with nitrogen and

sealed in a polyethylene tube. The tube was subjected to a dose of 2.5 MegaRads of ionising radiation from a Cobalt 60 source. The solid copolymer formed was very hard and transparent. The water absorption of the copolymer determined on a 3 mm. thick disc was 265% after immersion for three days. The disc was transparent, light amber in colour, very flexible and strong, and greatly swollen after immersion for eleven days. The polymerisation conversion was found to be greater than 98%.

Example 5

A polyamide of terephthalic acid and a mixture of 2,2,4- and 2,4,4-trimethylhexamethylene diamines was dissolved in N-vinyl-2-pyrrolidone so that the weight ratio of the polyamide to the N-vinyl-2-pyrrolidone was 1:3. The solution was subjected to an absorbed dose of 2 MegaRads of gamma ray radiation from a Cobalt 60 source, and a rigid transparent polymer was produced. The water absorption of this polymer was 230% after immersion for four days.

The polymer product produced was transparent, flexible and of high tensile strength and tear resistance, and was particularly suitable for use in contact lenses. The polymerisation conversion was found to be greater than 98%.

Example 6

The polyamide of terephthalic acid and a mixture of 2,2,4- and 2,4,4-trimethylhexamethylene diamines was dissolved in N-vinyl-2-pyrrolidone so that the weight ratio of the polyamide to the N-vinyl-2-pyrrolidone was 1:4. An amount of allyl methacrylate representing 1% by weight of the total mixture was dissolved in the mixture. The mixture was subjected to an absorbed dose of 2 MegaRads of gamma ray radiation from a Cobalt 60 source, and a rigid transparent polymer was produced. The water absorption of this polymer was 220% after immersion for three days. The polymerisation conversion was found to be greater than 98%.

The polymer product produced was transparent, flexible and of high tensile strength and tear resistance, and was particularly suitable for use in contact lenses.

Any residual stress in the material after polymerisation was relieved by heat treatment under vacuum at 120°C. for four hours. The colour of the polymer changed from light amber to yellow after this treatment.

The initial mixture used in any of the Examples 1 to 4, may be polymerised by the electromagnetic radiation in a mould to produce a lens, implant or article of complex shape without subsequent machining.

As has hereinbefore been indicated, the hydrophilic polymer products produced

according to the invention are very suitable for use in contact with living tissue. Thus many of the polymer products are suitable for use as contact lenses and for prosthetic use, for example as heat valves or inserts in the inner ear cavity or other surgical appliances or implants. Many of the polymer products are also suitable for use as dialysis membranes in artificial kidney machines, and as protective corneal fittings or membranes. Such protective corneal membranes or soft lenses are suitable for use when an eye has been injured or is in need of protection for any other reason and such corneal membrane may be made opaque. As hereinbefore stated, the hydrophilic polymer products may incorporate a medically or therapeutically active ingredient such as an antibiotic. Thus the protective membrane for the eye may include an antibiotic or other drug and so function not only as a protective membrane for the eye but also as a vehicle for the installation of a drug into the eye. The hydrophilic polymer products may also be used as carriers, for example carriers of drugs, for oral administration.

WHAT WE CLAIM IS:—

1. A method for the production of a hydrophilic polymer product, which comprises subjecting to polymerisation an initial mixture containing (1) at least one hydrophilic monomer selected from N-vinyl pyrrolidones and hydroxyalkyl methacrylates and at least one hydrophobic monomer selected from alkyl acrylates, alkyl methacrylates and styrene or (2) at least one of N-vinyl-2-pyrrolidone and hydroxyethyl methacrylate and at least one hydrophobic polymer selected from nylons, polyamides or terephthalic acid with one or more alkyl-substituted hexamethylene diamines, poly(alkyl acrylates), poly(alkyl methacrylates), polystyrenes, polyvinyl chloride and bisphenol A polycarbonate, the polymerisation being effected by means of electromagnetic radiation in the ultraviolet ray—gamma ray range in an environment free from any chemical polymerisation initiator and from any residue of such initiator.

2. A method according to claim 1, in which the radiation has a quantum energy in the range 60—100 MeV.

3. A method according to claim 1 or claim 2, in which the radiation is gamma rays.

4. A method according to claim 3, in which the source of the radiation is cobalt 60.

5. A method according to any one of claims 1 to 4, in which the radiation dosage employed is from 2 to 5 Megarads.

6. A method according to claim 5, in which the radiation dosage is substantially 2.5 Megarads.

7. A method according to any one of

- claims 1 to 6, in which the radiation is extended over a period of from 1 to 48 hours.
8. A method according to any one of claims 1 to 7, in which the polymer product contains up to 90% by weight of hydrophobic component.
9. A method according to claim 8, in which the polymer product contains not more than 40% by weight of hydrophobic component.
10. A method according to any one of claims 1 to 9, in which the hydrophobic monomer is methyl methacrylate.
11. A method according to any one of claims 1 to 9, in which the hydrophobic monomer is methyl acrylate.
12. A method according to any one of claims 1 to 9, in which the hydrophobic polymer is nylon 6; nylon 6,6; nylon 6,10; nylon 11 or nylon 12.
13. A method according to any one of claim 1 to 9, in which the hydrophobic polymer is a polyamide of terephthalic acid with a mixture of 2,2,4- and 2,4,4-trimethylhexamethylene diamines.
14. A method according to any one of claims 1 to 9, in which the hydrophobic polymer is poly(methyl methacrylate).
15. A method according to any one of claims 1 to 9, in which the hydrophobic polymer is poly(methyl acrylate).
16. A method according to any one of the preceding claims, in which the hydrophilic monomer is N-vinyl-2-pyrrolidone.
17. A method according to any one of claims 1 to 15, in which the hydrophilic monomer comprises 2-hydroxyethyl methacrylate.
18. A method according to any one of claims 1 to 15, in which the hydrophilic monomer comprises a hydroxypropyl methacrylate.
19. A method according to any one of claims 1 to 11 and 16 to 18, in which the molar ratio of the hydrophilic monomer to the hydrophobic monomer is from 10:1 to 1:2.
20. A method according to claim 19, in which said molar ratio is from 5:1 to 2:1.
21. A method according to claim 19 or claim 20, in which the hydrophilic monomer is N - vinyl - 2 - pyrrolidone and the hydrophobic monomer comprises methyl methacrylate.
22. A method according to any one of the preceding claims, in which the polymerisation is carried out in the presence of a cross-linking agent.
23. A method according to claim 22, in which the cross-linking agent is a compound containing at least 2 olefinic bonds per molecule.
24. A method according to claim 23, in which the cross-linking agent is allyl methacrylate, divinylbenzene or ethylene glycol dimethacrylate.
25. A method according to any one of the preceding claims, in which the polymerisation is carried out in the presence of a therapeutic substance.
26. A method according to any one of claims 1 to 24, in which the polymerisation is carried out in the presence of a dye-stuff.
27. A method according to any one of the preceding claims, carried out in an oxygen-free atmosphere.
28. A method according to any one of claims 1 to 26, carried out under an inert atmosphere.
29. A method according to claim 28, in which the inert atmosphere is that of nitrogen or a noble gas.
30. A method according to any one of claims 1 to 26, carried out in vacuo.
31. A method according to any one of the preceding claims, carried out in a mould.
32. A method for the production of a hydrophilic polymer product substantially as hereinbefore described with reference to any one of the Examples.
33. A hydrophilic polymer product whenever prepared by the method claimed in any one of the preceding claims.
34. A contact lens made of the polymer product claimed in claim 33.
35. A prosthetic device made of the polymer product claimed in claim 33.
36. A surgical implant or appliance made of the polymer product claimed in claim 33.
37. A protective corneal fitting made of the polymer product claimed in claim 33.
38. A membrane made of the polymer product claimed in claim 33.
39. A carrier for the oral administration of a drug, the carrier comprising a non-toxic polymer product claimed in claim 33.

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